DIPHERELINE PRODUCT INFORMATION

NAME OF THE MEDICINE

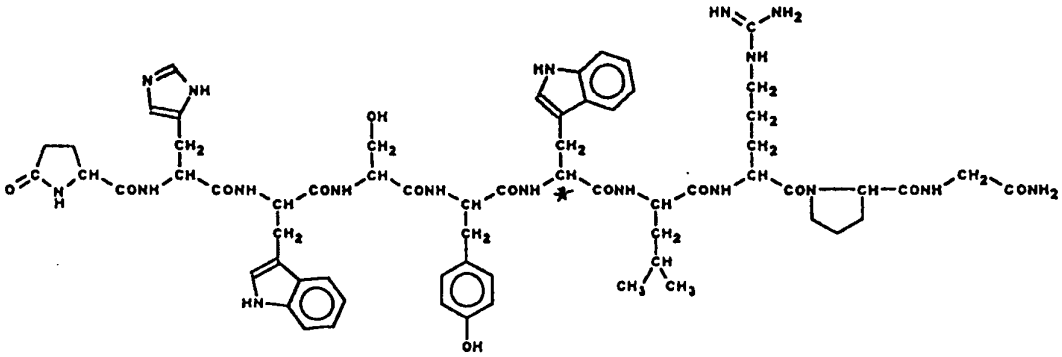
Triptorelin embonate

DESCRIPTION

Powder and solvent for suspension for injection, prolonged release granules.
White to off-white powder.

Structural formula:

[(L-Pyr)-(L-His)-(L-Trp)-(L-Ser)-(L-Tyr)-(D-Trp)-(L-Leu)-(L-Arg)-(L-Pro)-(Gly-NH_2)]



Molecular formula: $C_{64}H_{82}N_{18}O_{13}$ (triptorelin). $C_{23}H_{16}O_6$ (embonate)

Molecular weight: 1311.5 (triptorelin) + 388.4 (embonate)

CAS number: 57773-63-4

Diphereline 3.75mg 1 month formulation
Each vial contains a triptorelin content which allows the administration of an effective dose of 3.75 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 1.875 mg of triptorelin.

Diphereline 11.25mg 3 month formulation
Each vial contains a triptorelin content which allows the administration of an effective dose of 11.25 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 5.625 mg of triptorelin.

Diphereline 22.5mg 6 month formulation
Each vial contains a triptorelin content which allows the administration of an effective dose of 22.5 mg triptorelin. After reconstitution in 2 mL of solvent, 1 mL of reconstituted suspension contains 11.25 mg of triptorelin.

PHARMACOLOGY

Pharmacodynamics:

Triptorelin, a gonadotrophin releasing hormone (GnRH) agonist, inhibits gonadotrophin secretion when given continuously and in therapeutic doses. Male animal and human studies

show that after the administration of triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy. This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product.

In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

Pharmacokinetics:

Absorption:

In a sub-study of the pivotal efficacy trial DEB-96-TRI-01 of the 1- and 3-month doses, triptorelin exposure based on plasma AUC was comparable after intramuscular doses of the 1-month (x 3 doses at 28-day intervals) and 3-month formulations of triptorelin embonate (Table 1). Triptorelin did not accumulate over 9 months of treatment.

In a sub-study in 15 patients from the efficacy trial of the 6 month formulation (DEB-TRI6M-301), the plasma C_{max} after the first injection was comparable to that obtained previously with the 3-month formulation and higher than the 1-month formulation; however, the AUC over 6 months was about half that after the 3-month and 1-month formulations.

The relationship between serum triptorelin and serum testosterone is not linear but on/off, so the level of serum triptorelin rather than AUC is important in maintaining castrate serum testosterone levels. After an initial surge, mean ± SD serum testosterone remained below the castrate level (≤ 1.735 nmol/L) for the 336 days of the trial, except at Day 336 when the upper limit of the standard deviation was above the castrate level.

TABLE 1. PHARMACOKINETIC PARAMETERS OF 1-MONTH, 3-MONTH AND 6-MONTH FORMULATIONS OF TRIPTORELIN EMBONATE

Formulation	N	Geometric Mean (range) C_{max} *after 1st injection (ng/mL)*	Median (Range) T_{max} after 1st injection *(hours)*	Geometric Mean AUC over 6 months *(days.ng/mL)*
1-month (3.75 mg x 3 doses)	14	15.6 (9.1-25.2)	2 (2-4)	197.9 (101.8-452.6) ($AUC_{(169-253d)}$ x 2)
3-month (11.25 mg)	13	35.8 (16.5-57.4)	2 (1-4)	202.3 (117.6-325.2) ($AUC_{(169-253d)}$ x 2)
6-month (22.5mg)	15	40.0 (22.2-76.8)	3 (2-12)	111.5 (52.2-177.4) $AUC_{169-337d}$

In a study in healthy volunteers, the absolute bioavailability of an intramuscular dose of the 1-month formulation was 83%.

Distribution:
Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0.5 mg triptorelin is approximately 30 L in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

Biotransformation:
Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded within tissues or are rapidly further degraded in plasma, or cleared by the kidneys.

Elimination:
Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of intermediate-release triptorelin acetate 0.5 mg to 6 young healthy adult males (mean Cl_{creat} 150 mL/min), 42% of the dose was excreted in the urine as intact triptorelin. The mean triptorelin clearance was 212 mL/min.

Special populations:
In the intravenous study referred to under Elimination, patients with renal and liver impairment were also studied. There were 6 subjects in each group. Compared to young healthy adult males, mean triptorelin clearance was reduced by 43% in subjects with moderate renal impairment (mean Cl_{creat} 40 mL/min), 58% in subjects with severe renal impairment (mean Cl_{creat} 8.9 mL/min) and 73% in subjects with hepatic impairment (Child Pugh score 5-9) and a lower mean Cl_{creat} (90 mL/min) than young healthy adult males. Triptorelin exposure was increased 2- to 4-fold in patients with renal or hepatic impairment.

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150 mL/min) indicated that triptorelin was eliminated twice as fast in the young population. This is related to the fact that triptorelin clearance is correlated to total creatinine clearance, which is well known to decrease with age.

Because of the large safety margin of triptorelin and since Diphereline is a sustained release formulation, no dose adjustment is recommended in patients with renal or hepatic impairment.

Pharmacokinetic/pharmacodynamic relationship(s):
The pharmacokinetics/pharmacodynamics relationship of triptorelin is not straightforward to assess, since it is non-linear and time-dependent. Thus, after acute administration in naive subjects, triptorelin induces a dose-dependent increase of LH and FSH responses.

When administered as a sustained release formulation, triptorelin stimulates LH and FSH secretion during the first days post dosing and, in consequence, testosterone secretion. As shown by the results of the different bioequivalence studies, the maximal increase in testosterone is reached after around 4 days with an equivalent C_{max} which is independent from the release rate of triptorelin. This initial response is not maintained despite continuous exposure to triptorelin and is followed by a progressive decrease of testosterone levels. In this

case too, the extent of triptorelin exposure can vary markedly without affecting the overall effect on testosterone serum levels.

CLINICAL TRIALS

One pivotal, long-term (9 months), controlled, Phase III, multicentre study (DEB-96-TRI-01, first phase) compared the 3.75mg (1month) and 11.25mg (3 month) embonate formulations in 348 patients with advanced prostatic cancer. Patients in this study had histologically confirmed stage C (52.9% of patients) or D (46.8% of patients) prostate cancer with testosterone levels greater than 5nmol/L at baseline. The mean age of the 348 patients in the safety population was 70.5 years (range 45 to 96 years); mean age at onset of prostate cancer was 69.8 years (range 44 to 96 years) and the mean disease duration was 6.9 months (range 0 to 155 months).

Per protocol and intent-to-treat analyses produced similar results. The 3-month formulation was non-inferior (no worse than 10 percentage point difference in incidence) to the 1-month formulation in inducing and maintaining chemical castration (Table 2).

TABLE 2. CHEMICAL CASTRATION IN ADVANCED PROSTATE CANCER
Trial DEB-96-TRI-01 Phase 1 *per protocol* population.

Parameter	Triptorelin 11.25 mg q 12w (n=166)	Triptorelin 3.75 mg q 4w (n=159)	Difference [95% CI][4]
Induction by day 29[1,2]	97.6%	92.5%	5.1% [-1.1%, 13.8%]
Maintenance 2-9 mths[3]	94.1%	95.3%	-1.2% [-6.3%, 3.9%]
LH increase ≤ 1.0 IU/L – Day 85	92.5%	97.4%	-4.9% [-13.6%, 1.4%]
LH increase ≤ 1.0 IU/L – Day 169	92.4%	98.6%	-6.2% [-15.3%, -0.1%]*

[1] Serum testosterone < 1.735 nmol/L.
[2] Chemical castration was achieved by day 57 in most patients.
[3] Kaplan-Meier estimate.
[4] A lower bound > -10% demonstrates non-inferiority between treatments.
* 1-month formulation significantly better.

The second phase of study DEB-96-TRI-01 (9 months) compared the efficacy of the 1 month formulation of triptorelin 3.75 mg and the US 1 month formulation of leuprorelin acetate 7.5mg in patients with advanced prostatic cancer (the US formulation of leuprorelin acetate is not the same as the Australian-registered formulation). This study involved 284 patients who had histologically confirmed stage C or D prostatic cancer.

Per protocol and intent-to-treat analyses produced similar results. Whilst the 1-month formulation was slower in inducing chemical castration than the US 1-month leuprorelin acetate formulation, it was non-inferior in maintaining chemical castration (no worse than 10 percentage point difference in incidence) - Table3.

TABLE 3. CHEMICAL CASTRATION IN ADVANCED PROSTATE CANCER
Trial DEB-96-TRI-01 Phase 2 *per protocol* population.

Parameter	Triptorelin 3.75 mg q 4w (n=135)	Leuprorelin[5] 7.5 mg q 4w (n=137)	Difference [95% CI][4]
Induction by day 29[1,2]	91.1%	99.3%	-8.2% [-17.1%, 1.4%]*
Maintenance 2-9 mths[3]	96.1%	93.1%	3.0% [-2.5%, 8.6%]
LH increase ≤ 1.0 IU/L – Day 85	98.4%	93.6%	4.8% [-1.9%, 15.0%]
LH increase ≤ 1.0 IU/L – Day 169	98.3%	93.8%	4.5% [-3.0 %, 15.0%]

[1] Serum testosterone < 1.735 nmol/L.
[2] Chemical castration was achieved by day 57 in most patients.
[3] Kaplan-Meier estimate.
[4] A lower bound > -10% demonstrates non-inferiority between treatments.
[5] US formulation not available in Australia.
* Leuprorelin significantly better.

With continuous use, desensitisation of the pituitary gonadotrophin receptors had generally occurred by 84 days of exposure making a surge in serum testosterone unlikely after this time – Tables 2 & 3 show that most patients had minimal increases in serum LH (≤ 1.0 IU/L) at days 85 and 169.

In trial DEB-TRI6M-301, 120 patients with advanced prostate cancer received Diphereline 22.5 mg 6-month formulation IM on Days 1 and 169 and were followed until Day 337 (48 weeks). The median age of patients was 70 years (range 50 – 92). The primary efficacy endpoints were the percentage of patients achieving the castrate level of testosterone (≤ 1.735 nmol/L) by Day 29 and percentage of patients maintaining this level from day 57 to Week 48. 115 patients (96%) completed the study. Three patients died, one was lost to follow-up and one withdrew consent. Of the patients completing the trial, 93% maintained castrate serum testosterone levels from Day 57 to Week 48 (Table 4 per protocol population). Intent- to-treat results were similar.

TABLE 4. CHEMICAL CASTRATION IN ADVANCED PROSTATE CANCER
Trial DEB-TRI6M-301 *per protocol* population.

Parameter	Triptorelin 22.5 mg q 24w n = 115	95% CI
Induction by Day 29[1]	97.4 %	[92.6% , 99.5%]
Maintenance 2-9 months[2]	93.9 %	[89.5%, 98.3%]
Maintenance 2-12 months (48 weeks) [2]	93.0 %	[88.3%, 97.7%]
LH increase ≤ 1.0 IU/L – Day 169	98.2 % (n=114)	[93.8%, 99.8%]

[1] Serum testosterone ≤ 1.735 nmol/L.
2.Kaplan-Meier estimate.

INDICATIONS

Diphereline is indicated for the treatment of hormone-dependent locally advanced or metastatic prostate cancer.

CONTRAINDICATIONS

Diphereline is contraindicated in patients with known hypersensitivity to triptorelin, GnRH, other GnRH agonist analogues or to any of the excipients of Diphereline, in particular, polysorbate 80, which has been observed to induce hypersensitivity reactions in some patients.

Diphereline is contraindicated in patients with spinal cord compression secondary to prostate cancer metastases.

PRECAUTIONS

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (*see INTERACTIONS WITH OTHER MEDICINES*) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Diphereline.

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss. Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

Treatment with GnRH analogues may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present a pituitary apoplexy which is characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

Adjustment of antihypertensive therapy may be required in patients receiving such medication.

There is an increased risk of mood changes and incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

Initially triptorelin causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.

A small number of patients may experience a temporary worsening of signs and symptoms of prostate cancer (tumour flare) and a temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an

immediate orchiectomy should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every one, three or six months. The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

Caution is required with intramuscular injection in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

Administration of triptorelin in therapeutic doses results in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with a GnRH agonist may therefore be misleading.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

All formulations of Diphereline contain less than 1 mmol (23 mg) sodium per dose.

Hyperglycaemia and Diabetes

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for the treatment of hyperglycaemia or diabetes.

Cardiovascular Diseases

An increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratio, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and managed according to current clinical practice.

<u>Interaction with other Medicines</u>

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Diphereline with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (*see PRECAUTIONS*).

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins, caution should be given and it is recommended that the patient's hormonal status should be supervised.

In the absence of relevant data and as a precaution, hyperprolactinaemic medicinal products should not be prescribed concomitantly with Diphereline since hyperprolactinaemia reduces the number of pituitary GnRH receptors.

Use in children

Safety and efficacy of Diphereline has not been established in neonates, infants, children and adolescents, therefore Diphereline is not indicated for use in these populations.

Impaired renal or hepatic function

No dosage adjustment is necessary for patients with renal or hepatic impairment. Diphereline must be administered under the supervision of a physician.

Effects on fertility

In chronic toxicity studies at clinically relevant doses, triptorelin induced changes in the reproductive organs of male rats, dogs and monkeys. These were considered to reflect the suppressed gonadal function caused by the pharmacological activity of the compound. These changes would be expected to cause a profound impairment of fertility, but were partly reversed (males) or largely reversed (females) after cessation of treatment. In males, changes included decreases in weight and atrophic histological changes in the testes, epididymis, seminal vesicle and prostate gland, with suppression of spermatogenesis. In females, changes included ovarian atrophy and suppression of ovarian function, with arrest of follicular development and cessation of oestrus cycling; uterine weights were also reduced.

Genotoxicity

In vitro genotoxicity tests for gene mutations and chromosomal damage, and a mouse micronucleus test have provided no evidence for genotoxic effects.

Carcinogenicity

Carcinogenicity studies were conducted in mice (18 months) and rats (23 months) with triptorelin embonate microgranules administered once monthly IM. In mice, no oncogenic effect was observed at triptorelin doses of up to 6000 micrograms/kg/month. In rats, an almost 100% incidence of pituitary tumors was observed at each dose level (120, 600 and 3000 micrograms/kg/month), leading to premature death. There were increased incidences of both pituitary adenomas and carcinomas at all dose levels. The increased incidence of pituitary tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

Use in Pregnancy

Diphereline is not indicated for use in females. After subcutaneous administration of 10 micrograms/kg/day to rats on days 6 to 15 of gestation, triptorelin did not elicits any embryotoxicity or teratogenicity. At 100 micrograms/kg/day, a reduction in maternal body weight gain and an increased number of resorptions were observed.

Use in Lactation

Diphereline is not indicated for use in females.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence, epileptic seizures and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease

ADVERSE EFFECTS

Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are generally old and have other diseases frequently encountered in this aged population, most of the patients included in clinical trials reported adverse events. As seen with other GnRH agonist therapies or after surgical castration, the most commonly observed adverse events related to triptorelin treatment were due to its expected pharmacological effects: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects included hot flushes (50%), erectile dysfunction (4%) and decreased libido (3%).

With the exception of immuno-allergic reactions (0.2%) and injection site reactions (3%), all adverse reactions are known to be related to testosterone changes.

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these are known to be related to biochemical or surgical castration.

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000). No very rare (<1/10000) adverse reactions were reported.

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare*	*Additional post-marketing adverse events*
	≥ 10%	*≥1% - <10%*	*≥0.1% - <1%*	*≥0.01% - <0.1%*	
Blood and lymphatic system disorders			Thrombocytosis		
Cardiac disorders			Palpitations		QT prolongation (see *Interactions with other Medicines* and *Precautions*)
Ear and labyrinth disorders			Tinnitus Vertigo		
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Gastrointestinal disorders		Nausea Dry mouth	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
General disorders and administration site conditions	Asthenia	Injection site erythema, inflammation, pain, reaction	Lethargy Oedema peripheral Pain	Chest pain Dysstasia Influenza like illness	Malaise

		Oedema	Rigors Somnolence	Pyrexia	
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Infections and infestations				Nasopharyngitis	
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Musculoskeletal and connective tissue disorders	Back pain	Musculo-skeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Gynaecomastia Breast pain Testicular atrophy Testicular pain		
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Skin and	Hyperhydrosis		Acne	Blister	Angioneurotic

subcutaneous tissue disorders			Alopecia Erythema Pruritus Rash Urticaria	Purpura	oedema
Vascular disorders	Hot flush	Hypertension		Hypotension	

** This frequency is based on class-effect frequencies common for all GnRH agonists.*

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the sustained release formulation. With this initial increase in circulating testosterone levels, a small percentage of patients (≤ 5%) may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare), usually manifested by an increase in urinary symptoms (< 2%) and metastatic pain (5%), which can be managed symptomatically. Isolated cases of exacerbation of disease symptoms, either urethral obstruction or spinal cord compression by metastasis have occurred. Therefore, patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (*see PRECAUTIONS*).

The use of synthetic GnRH agonists, to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

Increased lymphocyte count has been reported with patients undergoing GnRH analogue treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Uncommonly pressure sensitive infiltrations at the injection site have been reported in other triptorelin products after subcutaneous injection.

Reporting of suspected adverse effects

Reporting suspected adverse effects after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse effects via the TGA Adverse Drug Reactions System (ADRS).

DOSAGE AND ADMINISTRATION

Diphereline 3.75mg 1month formulation
The recommended dose of Diphereline is 3.75 mg triptorelin (1 vial) administered once a month as a single intramuscular injection.

Diphereline 11.25mg 3 month formulation
The recommended dose of Diphereline is 11.25 mg triptorelin (1 vial) administered every three months as a single intramuscular injection.

Diphereline 22.5mg 6 month formulation
The recommended dose of Diphereline is 22.5 mg triptorelin (1 vial) administered every six months as a single intramuscular injection.

The lyophilised microgranules are to be reconstituted using 2 mL sterile water for injection (*see METHOD OF ADMINISTRATION*). The injection site should be varied periodically.

Since Diphereline is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Method of Administration

The solvent for suspension should be drawn into the injection syringe and transferred to the vial containing the powder. The vial should be gently shaken to thoroughly disperse particles and obtain a uniform suspension. The suspension will appear milky. The suspension obtained should be drawn back into the injection syringe. The injection needle has to be changed and the produced suspension for injection should be administered immediately.

The suspension should be discarded if not used immediately after reconstitution.

Diphereline contains no antimicrobial agent. The product is for treatment of one patient only on one occasion. Discard any remaining contents. Used injection needles should be disposed in a designated sharp container. Any remaining product should be discarded.

OVERDOSAGE

The pharmaceutical properties of Diphereline and its route of administration make accidental or intentional overdose unlikely. There is no human experience of overdose. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Diphereline. If overdose occurs, symptomatic management is indicated. If you feel you may have been given too much Diphereline, contact the Poisons Advisory Centre on 131126 for advice on management.

PRESENTATION and STORAGE

Diphereline 3.75 mg 1 month formulation
Approximately 288 mg of white to off-white powder in 6 mL type I brown tint glass vial with grey bromobutyl stopper and purple aluminum flip-off capsule.

Diphereline 11.25 mg 3 month formulation
Approximately 273 mg of white to off-white powder in 6 mL type I brown tint glass vial with grey bromobutyl stopper and yellow green aluminum flip-off capsule.

Diphereline 22.5 mg 6 month formulation
Approximately 365 mg of white to off-white powder in 6 mL type I brown tint glass vial with grey bromobutyl stopper and dark green aluminum flip-off capsule.

Solvent: Type I glass ampoule containing 2 mL of sterile solvent for suspension.
Each box contains 1 vial, 1 ampoule and 1 blister containing 1 empty polypropylene injection syringe and 2 injection needles.
Composition of the Powder: polyglactin, mannitol , carmellose sodium, polysorbate 80.
Composition of the Solvent: Water for Injections.

Storage

Store the product and solvent below 25ºC.
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.
From a microbiological point of view, the prepared suspension should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC.

POISON SCHEDULES: S4

SPONSOR
Ipsen Pty Ltd
Level 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

AUST R 109854: Diphereline 3.75 mg 1 month formulation
AUST R 109856: Diphereline 11.25 mg 3 month formulation
AUST R 159173: Diphereline 22.5 mg 6 month formulation

Date of first inclusion in ARTG: 28 August 2006
Date of most recent amendment: 24 February 2015